

Supporting Information for:

A Room-Temperature Alternative to the Arbuzov
Reaction: the Reductive Deoxygenation of Acyl
Phosphonates

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Chemistry—General.

All reactions were performed under argon using solvents that were dried and purified according to the method of Pangborn et al.ⁱ All flasks and vials were oven dried at 122°C and cooled in a desiccator box containing anhydrous calcium sulfate. But for the exceptions listed here, commercial reagents were purified according to the methods compiled by Armengo and Perrin.ⁱⁱ Potassium t-butoxide, anhydrous t-butanol, and 1.0 M hydrazine in THF solution were used as purchased from Aldrich without further purification and stored under argon. Hydrocinamic acids that could not be purchased were synthesized from the corresponding benzaldehyde according to a literature procedure.ⁱⁱⁱ Reactions were monitored by thin-layer chromatography on Merck Siligel 60-F₂₅₄. Compounds were visualized with a UV lamp (254 nm) and stained with potassium permanganate solution. Column chromatography was carried out in accordance with the methods of Still et al.^{iv} using EMD-Merck silica gel 60, 230-400 mesh ASTM. ¹H, ³¹P and ¹³C NMR spectra were acquired on a Varian Mercury 300 MHz spectrometer. High-resolution mass spectrometry was performed on a JEOL JMS-600H HRMS using an Electrospray Ion Source.

Chemistry—Synthesis.

Diethyl ethylphosphonate (Table 1, entry 1). Acetyl chloride (72 μL, 1 mmol) was added to dichloromethane (8 mL) in a 25 mL roundbottomed flask and cooled on an icebath. Triethylphosphite (171 μL, 1 mmol) was then added dropwise to this chilled solution under stirring, then the reaction was allowed to come to room temperature. After two hours stirring, the reaction was reduced *in vacuo*, and benzoic acid (245 mg, 2 mmol) was added directly to the residue, followed by benzene (10 mL). The mixture was stirred to dissolve completely, then hydrazine solution (1.05 mL, 1.0 M in THF, 1.05 mmol) was added dropwise under rapid stirring. After 90 minutes, the reaction was flash-frozen and lyophilized. After lyophilization, 1:1 v/v tetrahydrofuran:*tert*-butanol (10 mL) was added to the flask and stirred to dissolve the solid. Potassium *tert*-butoxide solution (5 mL, 0.6 M in 1:1 v/v tetrahydrofuran:*tert*-butanol, 3 mmol) was then added to the stirring solution in one portion. After 6 h room temperature stirring, the reaction was diluted with ethyl acetate (50 mL), quenched with 1 N HCl (20 mL), washed with saturated sodium bicarbonate (2 x 15 mL), then with brine (15 mL), dried on sodium sulfate, reduced *in vacuo*, then purified by flash chromatography on silica (15% acetone in dichloromethane) to give the desired product as a colorless liquid; 97.0 mg (58.4%). ¹H NMR (300 MHz, CDCl₃) δ 3.98-4.12 (m, 4H), 1.62-1.68, (dq, 2H, *J* = 18.2, 7.8 Hz), 1.28 (t, 3H, *J* = 7.1 Hz), 1.11 (dt, 6H, *J* = 20.0, 7.8 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 61.4, 61.3, 19.7, 17.8, 16.4, 16.5, 6.5, 6.4; ³¹P NMR (121 MHz, CDCl₃) δ 33.6; HRMS (FAB⁺) calculated for [C₆H₁₆O₃P] ([M+H]⁺) 167.0837, found 167.0836.^v

Diethyl propylphosphonate. (Table 1, entry 2). Propionyl chloride (87 μL, 1 mmol) was added to dichloromethane (8 mL) in a 25 mL roundbottomed flask and cooled on an icebath. Triethylphosphite (171 μL, 1 mmol) was then added dropwise to this chilled solution under stirring, then the reaction was allowed to come to room temperature. After one hour stirring, the reaction was reduced *in vacuo*, and benzoic acid (245 mg, 2 mmol) was added directly to the residue, followed by benzene (10 mL). The mixture was stirred to dissolve completely, then

hydrazine solution (1.05 mL, 1.0 M in THF, 1.05 mmol) was added dropwise under rapid stirring. After 60 minutes, the reaction was flash-frozen and lyophilized. After lyophilization, 1:1 v/v tetrahydrofuran:*tert*-butanol (10 mL) was added to the flask and stirred to dissolve the solid. Potassium *tert*-butoxide solution (5 mL, 0.6 M in 1:1 v/v tetrahydrofuran:*tert*-butanol, 3 mmol) was then added to the stirring solution in one portion. After 6 h room temperature stirring, the reaction was diluted with ethyl acetate (50 mL), quenched with 1 N HCl (20 mL), washed with saturated sodium bicarbonate (2 x 15 mL), then with brine (15 mL), dried on sodium sulfate, reduced *in vacuo*, then purified by flash chromatography on silica (10% acetone in dichloromethane) to give the desired product as a colorless liquid; 133.8 mg (74.3 %). ¹H NMR (300 MHz, CDCl₃) δ 3.93-4.11 (m, 4H), 1.48-1.70, (m, 4H), 1.25 (t, 6H, *J* = 7.1 Hz), 0.92-0.97 (m, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 61.3, 61.2, 28.6, 26.7, 16.4, 16.3, 16.1, 16.0, 15.3, 15.1; ³¹P NMR (121 MHz, CDCl₃) δ 32.2; HRMS (FAB⁺) calculated for [C₇H₁₈O₃P] ([M+H]⁺) 181.0994, found 181.1003.^{vi}

Diethyl *sec*-butylphosphonate. (Table 1, entry 3b). 2-Methylpropionyl chloride (106 mg, 1 mmol) was added to dichloromethane (8 mL) in a 25 mL roundbottomed flask and cooled on an icebath. Triethylphosphite (171 μL, 1 mmol) was then added dropwise to this chilled solution under stirring, then the reaction was allowed to come to room temperature. After one hour stirring, the reaction was reduced *in vacuo*, and benzoic acid (500 mg, 4 mmol) was added directly to the residue, followed by benzene (10 mL). The mixture was stirred to dissolve completely, then hydrazine solution (1.05 mL, 1.0 M in THF, 1.05 mmol) was added dropwise under rapid stirring. After 60 minutes, the reaction was flash-frozen and lyophilized. After lyophilization, 1:1 v/v tetrahydrofuran:*tert*-butanol (7 mL) was added to the flask and stirred to dissolve the solid. Potassium *tert*-butoxide solution (8 mL, 0.6 M in 1:1 v/v tetrahydrofuran:*tert*-butanol, 5 mmol) was then added to the stirring solution in one portion. After 12 h room temperature stirring, the reaction was diluted with ethyl acetate (50 mL), quenched with 1 N HCl (20 mL), washed with saturated sodium bicarbonate (2 x 15 mL), then with brine (15 mL), dried on sodium sulfate, reduced *in vacuo*, then purified by flash chromatography on silica (12% acetone in dichloromethane) to give the desired product as a colorless liquid; 88.5 mg (45.6 %). ¹H NMR (300 MHz, CDCl₃) δ 3.96-4.14 (m, 4H), 1.95-2.12 (m, 1H), 1.63 (dd, 2H, *J* = 18.2, 6.8 Hz), 1.28 (t, 6H, *J* = 7.1 Hz), 1.01 (dd, 6H *J* = 6.7, 1.0 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 61.2, 61.1, 35.4, 33.6, 24.1, 24.0, 23.7, 23.7, 16.5, 16.4; ³¹P NMR (121 MHz, CDCl₃) δ 31.6; HRMS (FAB⁺) calculated for [C₈H₂₀O₃P] ([M+H]⁺) 195.1150, found 195.1173.^{vii}

Diethyl benzylphosphonate. (Table 1, entry 5b). Benzoyl chloride (117 μL, 1 mmol) was added to dichloromethane (8 mL) in a 25 mL roundbottomed flask and cooled on an icebath. Triethylphosphite (171 μL, 1 mmol) was then added dropwise to this chilled solution under stirring, then the reaction was allowed to come to room temperature. After one hour stirring, the reaction was reduced *in vacuo*, and *ortho*-bromobenzoic acid (400 mg, 2 mmol) was added directly to the residue, followed by benzene (10 mL). The mixture was stirred, then hydrazine solution (1.05 mL, 1.0 M in THF, 1.05 mmol) was added dropwise under rapid stirring. After 6 hours, the reaction was flash-frozen and lyophilized. After lyophilization, 1:1 v/v tetrahydrofuran:*tert*-butanol (10 mL) was added to the flask and stirred to dissolve the solid. Potassium *tert*-butoxide solution (5 mL, 0.6 M in 1:1 v/v tetrahydrofuran:*tert*-butanol, 3 mmol) was then added to the stirring solution in one portion. After 4 h room temperature stirring, the reaction was diluted with ethyl acetate (50 mL), quenched with 1 N HCl (20 mL), washed with

saturated sodium bicarbonate (2 x 15 mL), then with brine (15 mL), dried on sodium sulfate, reduced *in vacuo*, then purified by flash chromatography on silica (15% acetone in dichloromethane) to give the desired product as a colorless liquid; 68.6 mg (30.1 %). ¹H NMR (300 MHz, CDCl₃) δ 7.23-7.31 (m, 5H), 3.95-4.06 (m, 4H), 3.15 (d, 2H, *J* = 21.6 Hz), 1.24 (t, 6H, *J* = 7.1 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 131.6, 131.6, 129.8, 129.7, 128.5, 128.5, 126.9, 126.8, 62.1, 62.1, 34.3, 33.2, 16.4, 16.3; ³¹P NMR (121 MHz, CDCl₃) δ 26.4; HRMS (FAB⁺) calculated for [C₁₁H₁₈O₃P] ([M+H]⁺) 229.0994, found 229.1005.^{viii}

Diethyl 2-phenylethylphosphonate. (Table 1, entry 6). Phenylacetyl chloride (154 mg, 1 mmol) was added to dichloromethane (8 mL) in a 25 mL roundbottomed flask and cooled on an icebath. Triethylphosphite (171 μL, 1 mmol) was then added dropwise to this chilled solution under stirring, then the reaction was allowed to come to room temperature. After two hours stirring, the reaction was reduced *in vacuo*, and benzoic acid (245 mg, 2 mmol) was added directly to the residue, followed by benzene (10 mL). The mixture was stirred to dissolve completely, then hydrazine solution (1.05 mL, 1.0 M in THF, 1.05 mmol) was added dropwise under rapid stirring. After 60 minutes, the reaction was flash-frozen and lyophilized. After lyophilization, 1:1 v/v tetrahydrofuran:*tert*-butanol (10 mL) was added to the flask and stirred to dissolve the solid. Potassium *tert*-butoxide solution (5 mL, 0.6 M in 1:1 v/v tetrahydrofuran:*tert*-butanol, 3 mmol) was then added to the stirring solution in one portion. After 6 h room temperature stirring, the reaction was diluted with ethyl acetate (50 mL), quenched with 1 N HCl (20 mL), washed with saturated sodium bicarbonate (2 x 15 mL), then with brine (15 mL), dried on sodium sulfate, reduced *in vacuo*, then purified by flash chromatography on silica (15% acetone in dichloromethane) to give the desired product as a yellow liquid; 158.1 mg (65.3 %). ¹H NMR (300 MHz, CDCl₃) δ 7.16-7.30 (m, 5H), 4.03-4.13 (m, 4H), 2.85-2.94 (m, 2H), 1.98-2.10 (m, 2H), 1.30 (t, 6H *J* = 7.0 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 141.1, 140.8, 128.5, 128.0, 126.3, 61.6, 61.5, 28.6, 28.5, 28.5, 26.6, 16.5, 16.4; ³¹P NMR (121 MHz, CDCl₃) δ 30.8; HRMS (FAB⁺) calculated for [C₁₂H₂₀O₃P] ([M+H]⁺) 243.1150, found 243.1158.⁸

Diethyl 3-phenylpropyl-1-phosphonate. (Table 1, entry 7). 3-Phenylpropionyl chloride (149 μL, 1 mmol) was added to dichloromethane (8 mL) in a 25 mL roundbottomed flask and cooled on an icebath. Triethylphosphite (171 μL, 1 mmol) was then added dropwise to this chilled solution under stirring, then the reaction was allowed to come to room temperature. After two hours stirring, the reaction was reduced *in vacuo*, and benzoic acid (245 mg, 2 mmol) was added directly to the residue, followed by benzene (10 mL). The mixture was stirred to dissolve completely, then hydrazine solution (1.05 mL, 1.0 M in THF, 1.05 mmol) was added dropwise under rapid stirring. After 90 minutes, the reaction was flash-frozen and lyophilized. After lyophilization, 1:1 v/v tetrahydrofuran:*tert*-butanol (10 mL) was added to the flask and stirred to dissolve the solid. Potassium *tert*-butoxide solution (5 mL, 0.6 M in 1:1 v/v tetrahydrofuran:*tert*-butanol, 3 mmol) was then added to the stirring solution in one portion. After 6 h room temperature stirring, the reaction was diluted with ethyl acetate (50 mL), quenched with 1 N HCl (20 mL), washed with saturated sodium bicarbonate (2 x 15 mL), then with brine (15 mL), dried on sodium sulfate, reduced *in vacuo*, then purified by flash chromatography on silica (100% ethyl acetate) to give the desired product as a faintly yellow liquid; 189.0 mg (73.8 %). ¹H NMR (300 MHz, CDCl₃) δ 7.12-7.28 (m, 5H), 3.95-4.12 (m, 4H), 2.64-2.69 (t, 2H, *J* = 7.4 Hz), 1.84-1.97 (m, 2H), 1.64-1.75 (m, 2H), 1.27 (t, 6H *J* = 7.1 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 141.0, 141.0, 128.4, 128.3, 126.0, 61.4, 61.3, 36.5, 36.3, 26.0, 24.2, 24.1, 24.1, 16.5, 16.4; ³¹P NMR

(121 MHz, CDCl₃) δ 32.0; HRMS (FAB⁺) calculated for [C₁₃H₂₂O₃P] ([M+H]⁺) 257.1307, found 257.1302.⁸

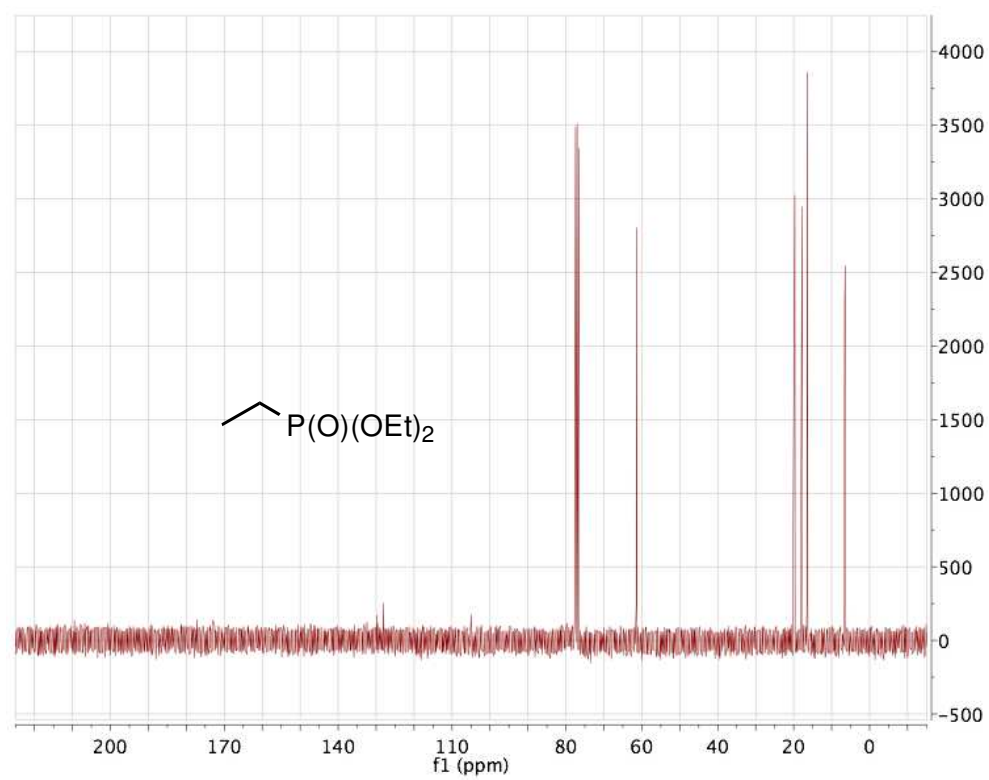
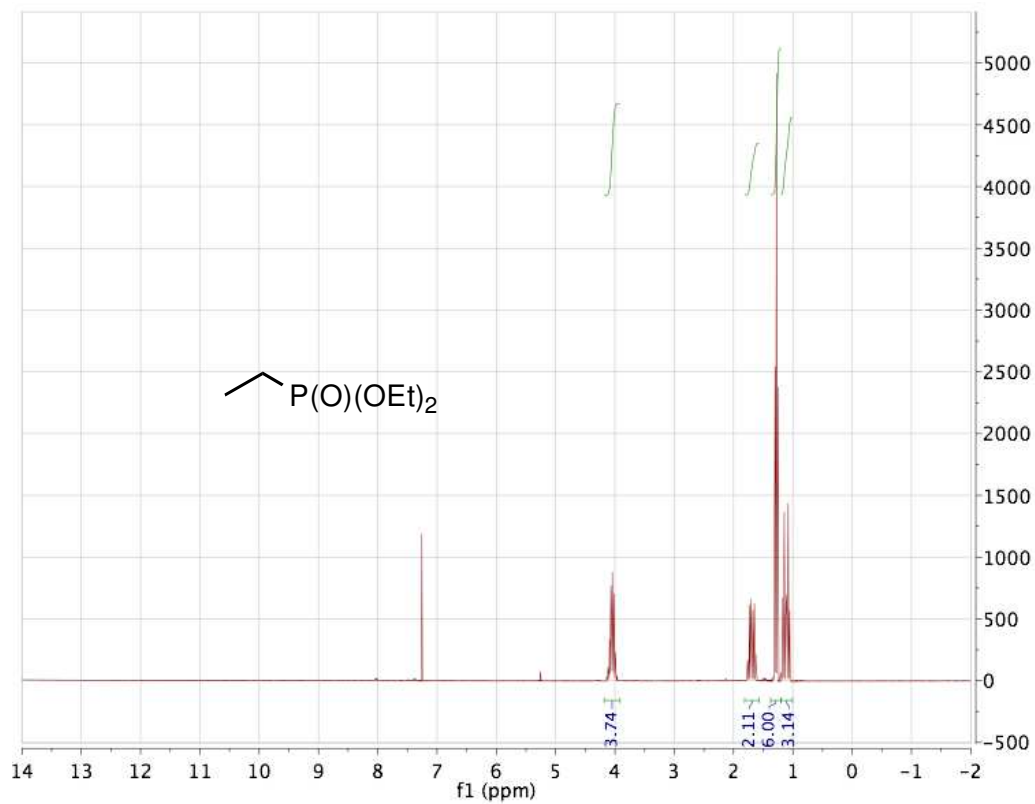
Diethyl 3-phenylpropyl-1-phosphonate. (Table 1, entry 8). 3-Phenylpropionic acid (150 mg, 1 mmol) was dissolved in dichloromethane (10 mL) in a 25 mL roundbottomed flask and cooled on an icebath. Oxalyl chloride (100 μ L, 1.2 mmol) was added in one portion under stirring, and the reaction was allowed to come to room temperature. After 12 hours the reaction was reduced *in vacuo*, then the residue was redissolved in dichloromethane (8 mL) and cooled on an icebath. Triethylphosphite (171 μ L, 1 mmol) was then added dropwise to this chilled solution under stirring, then the reaction was allowed to come to room temperature. After two hours stirring, the reaction was reduced *in vacuo*, and benzoic acid (245 mg, 2 mmol) was added directly to the residue, followed by benzene (10 mL). The mixture was stirred to dissolve completely, then hydrazine solution (1.05 mL, 1.0 M in THF, 1.05 mmol) was added dropwise under rapid stirring. After 90 minutes, the reaction was flash-frozen and lyophilized. After lyophilization, 1:1 v/v tetrahydrofuran:*tert*-butanol (10 mL) was added to the flask and stirred to dissolve the solid. Potassium *tert*-butoxide solution (5 mL, 0.6 M in 1:1 v/v tetrahydrofuran:*tert*-butanol, 3 mmol) was then added to the stirring solution in one portion. After 6 h room temperature stirring, the reaction was diluted with ethyl acetate (50 mL), quenched with 1 N HCl (20 mL), washed with saturated sodium bicarbonate (2 x 15 mL), then with brine (15 mL), dried on sodium sulfate, reduced *in vacuo*, then purified by flash chromatography on silica (100% ethyl acetate) to give the desired product as a faintly yellow liquid; 177.0 mg (69.1 %). ¹H NMR (300 MHz, CDCl₃) δ 7.15-7.30 (m, 5H), 3.97-4.15 (m, 4H), 2.66-2.71 (t, 2H, *J* = 7.4 Hz), 1.84-1.99 (m, 2H), 1.66-1.78 (m, 2H), 1.29 (t, 6H *J* = 7.1 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 141.0, 141.0, 128.5, 128.4, 126.0, 61.4, 61.3, 36.5, 36.3, 26.0, 24.2, 24.1, 16.5, 16.4; ³¹P NMR (121 MHz, CDCl₃) δ 32.0; HRMS (FAB⁺) calculated for [C₁₃H₂₂O₃P] ([M+H]⁺) 257.1307, found 257.1302.

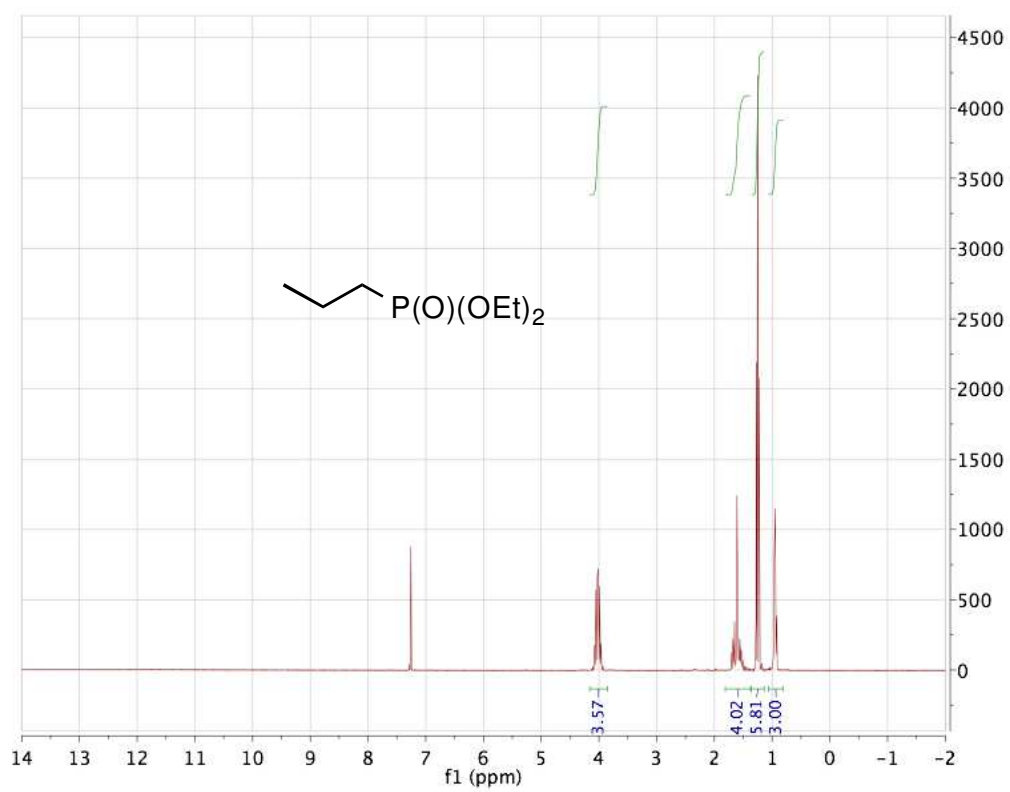
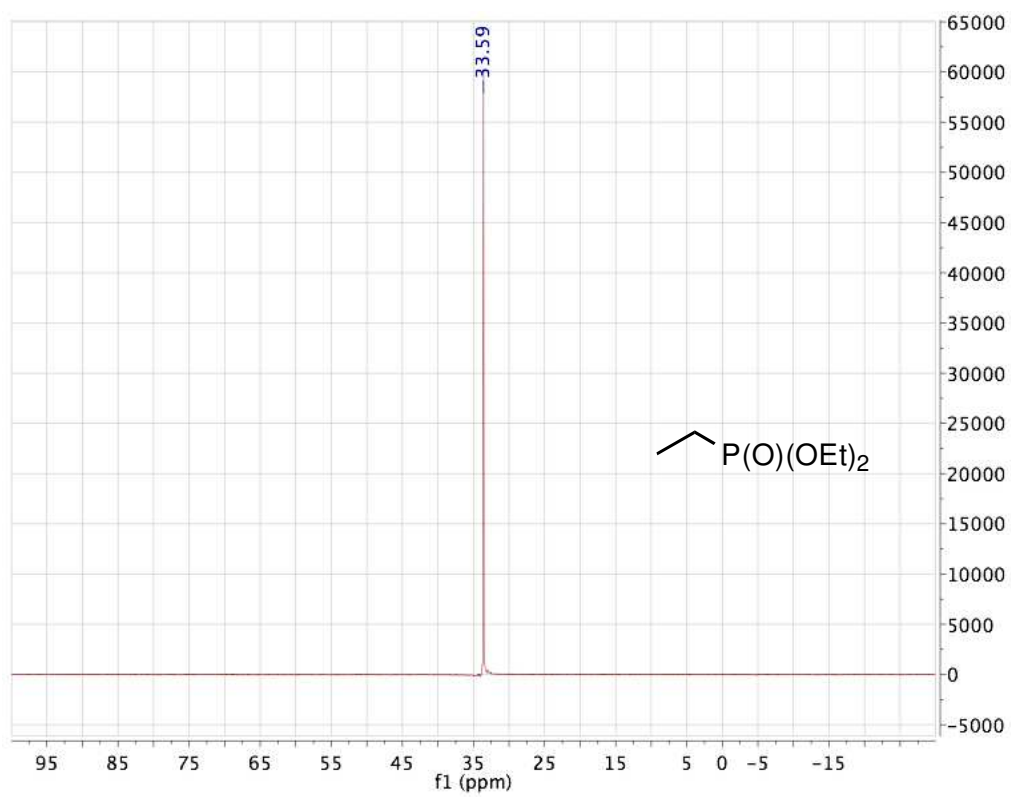
Diethyl 3-(4-methoxyphenyl)propyl-1-phosphonate. (Table 1, entry 9). 3-(4-methoxyphenyl)propionic acid (180 mg, 1 mmol) was dissolved in dichloromethane (10 mL) in a 25 mL roundbottomed flask and cooled on an icebath. Oxalyl chloride (100 μ L, 1.2 mmol) was added in one portion under stirring, and the reaction was allowed to come to room temperature. After 12 hours the reaction was reduced *in vacuo*, then the residue was redissolved in dichloromethane (8 mL) and cooled on an icebath. Triethylphosphite (171 μ L, 1 mmol) was then added dropwise to this chilled solution under stirring, then the reaction was allowed to come to room temperature. After two hours stirring, the reaction was reduced *in vacuo*, and benzoic acid (245 mg, 2 mmol) was added directly to the residue, followed by benzene (10 mL). The mixture was stirred to dissolve completely, then hydrazine solution (1.05 mL, 1.0 M in THF, 1.05 mmol) was added dropwise under rapid stirring. After 90 minutes, the reaction was flash-frozen and lyophilized. After lyophilization, 1:1 v/v tetrahydrofuran:*tert*-butanol (10 mL) was added to the flask and stirred to dissolve the solid. Potassium *tert*-butoxide solution (5 mL, 0.6 M in 1:1 v/v tetrahydrofuran:*tert*-butanol, 3 mmol) was then added to the stirring solution in one portion. After 6 h room temperature stirring, the reaction was diluted with ethyl acetate (50 mL), quenched with 1 N HCl (20 mL), washed with saturated sodium bicarbonate (2 x 15 mL), then with brine (15 mL), dried on sodium sulfate, reduced *in vacuo*, then purified by flash chromatography on silica (100% ethyl acetate) to give the desired product as a faintly yellow liquid; 187.4 mg (65.5 %). ¹H NMR (300 MHz, CDCl₃) δ 7.03-7.06 (m, 2H), 6.77-6.80 (m, 2H), 3.94-4.12 (m, 4H), 3.74 (s, 3H), 2.60 (t, 2H, *J* = 7.4 Hz), 1.79-1.93 (m, 2H), 1.62-1.75 (m, 2H),

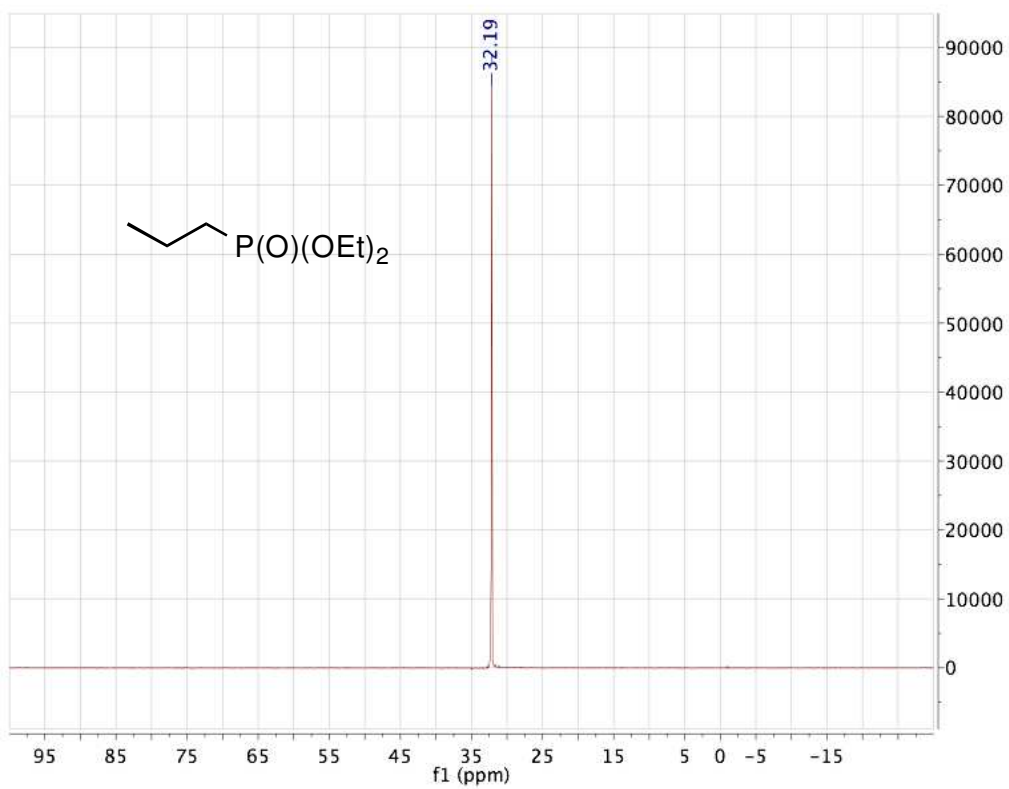
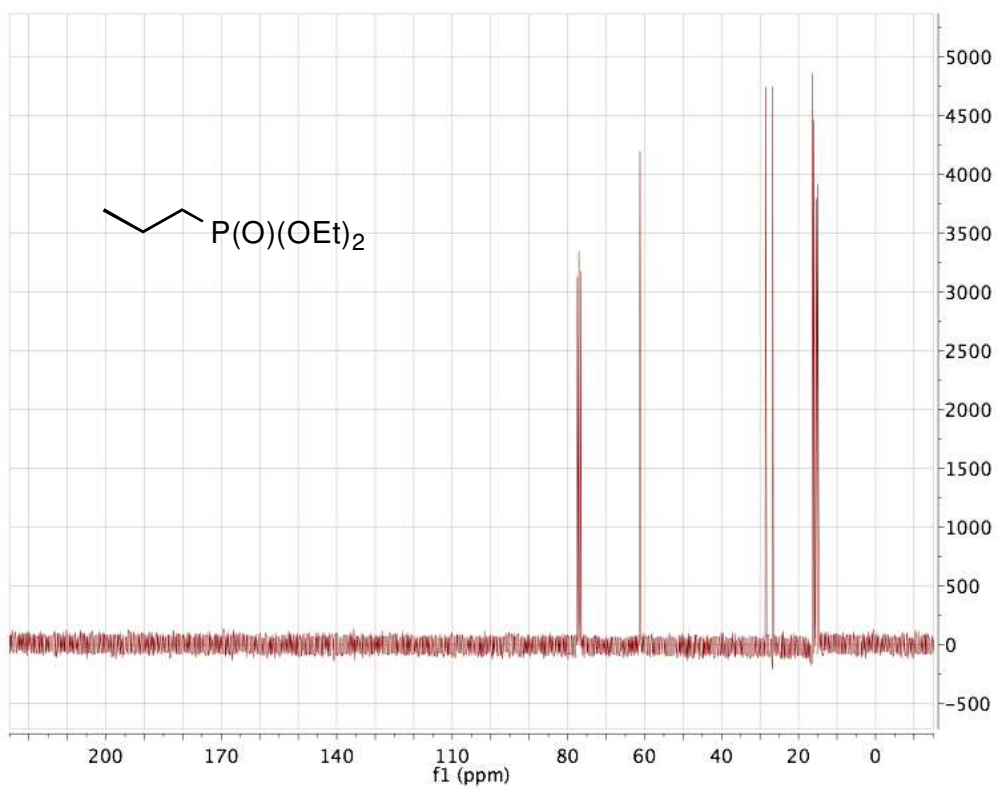
1.27 (t, 6H $J = 7.1$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 157.9, 133.1, 133.0, 129.3, 113.8, 61.4, 61.3, 55.2, 35.6, 35.4, 25.9, 24.3, 24.3, 24.0, 16.5, 16.4; ^{31}P NMR (121 MHz, CDCl_3) δ 32.2; HRMS (FAB^+) calculated for $[\text{C}_{14}\text{H}_{23}\text{O}_4\text{P}]$ ($[\text{M}+\text{H}]^+$) 286.1334, found 286.1342.

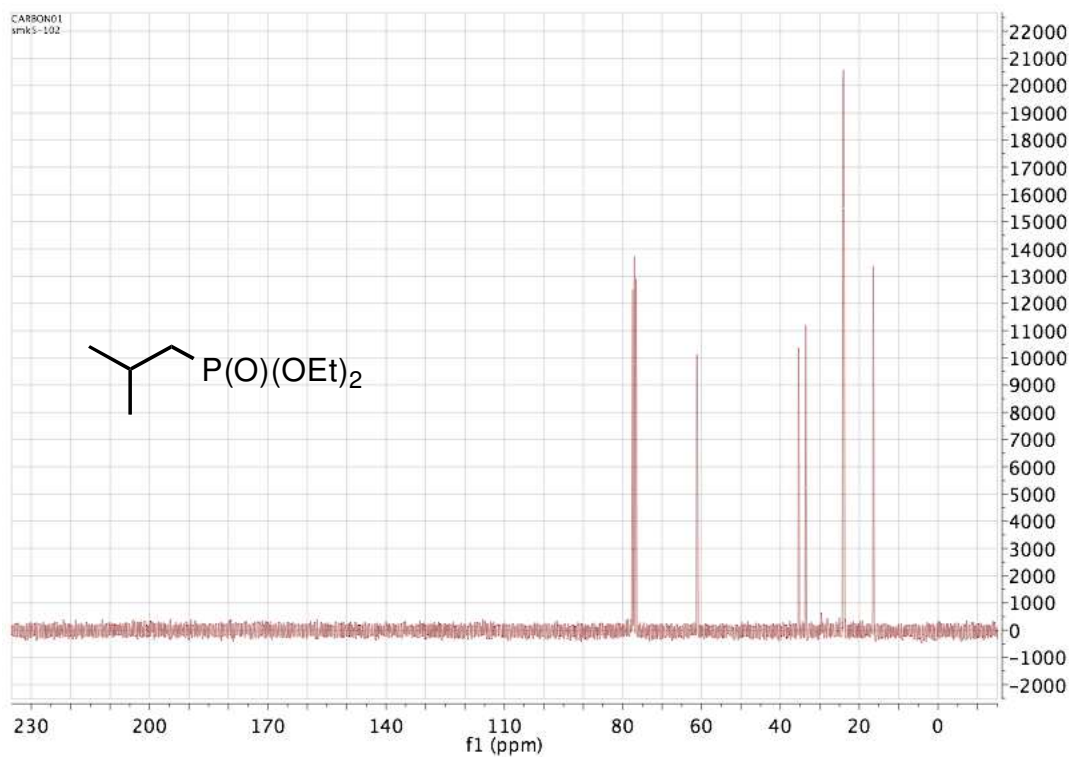
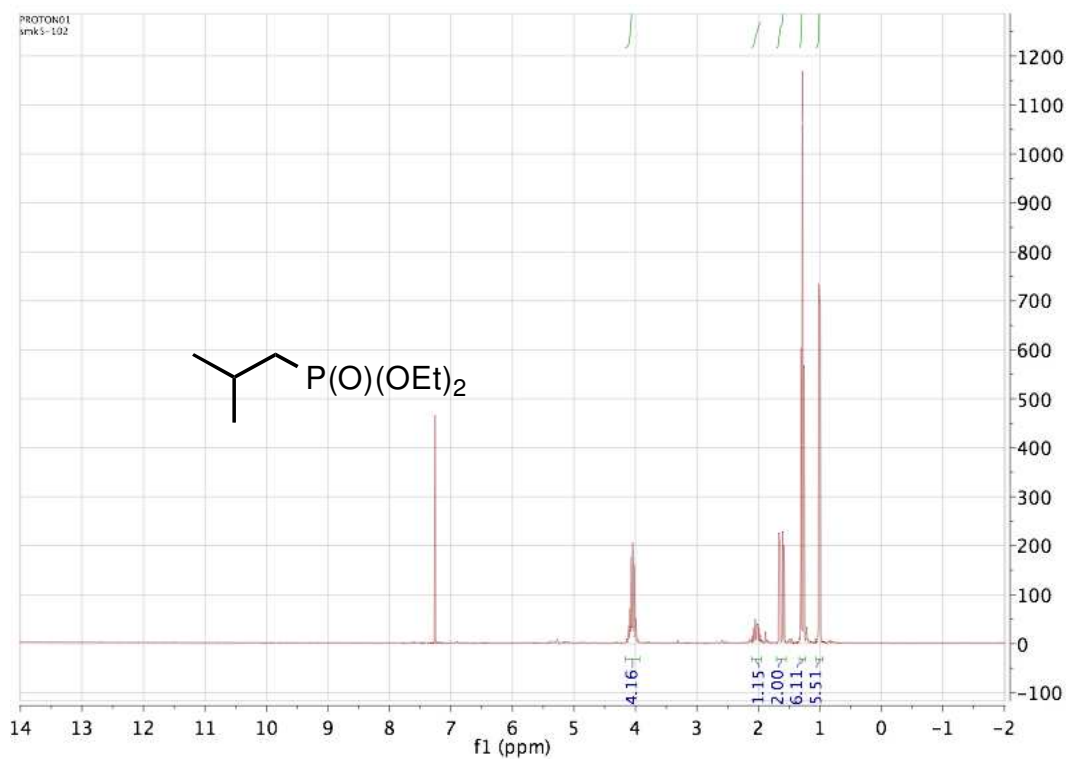
Diethyl 3-(4-cyanophenyl)propyl-1-phosphonate. (Table 1, entry 10). 3-(4-cyanophenyl) propionic acid (175 mg, 1 mmol) was dissolved in dichloromethane (10 mL) in a 25 mL roundbottomed flask and cooled on an icebath. A drop of dimethylformamide was added. Oxalyl chloride (100 μL , 1.2 mmol) was added in one portion under stirring, and the reaction was allowed to come to room temperature. After 12 hours the reaction was reduced *in vacuo*, then the residue was redissolved in dichloromethane (8 mL) and cooled on an icebath. Triethylphosphite (171 μL , 1 mmol) was then added dropwise to this chilled solution under stirring, then the reaction was allowed to come to room temperature. After two hours stirring, the reaction was reduced *in vacuo*, and benzoic acid (245 mg, 2 mmol) was added directly to the residue, followed by benzene (10 mL). The mixture was stirred to dissolve completely, then hydrazine solution (1.05 mL, 1.0 M in THF, 1.05 mmol) was added dropwise under rapid stirring. After 90 minutes, the reaction was flash-frozen and lyophilized. After lyophilization, 1:1 v/v tetrahydrofuran:*tert*-butanol (10 mL) was added to the flask and stirred. Potassium *tert*-butoxide solution (5 mL, 0.6 M in 1:1 v/v tetrahydrofuran:*tert*-butanol, 3 mmol) was then added to the stirring mixture in one portion. After 6 h room temperature stirring, the reaction was diluted with ethyl acetate (50 mL), quenched with 1 N HCl (20 mL), washed with saturated sodium bicarbonate (2 x 15 mL), then with brine (15 mL), dried on sodium sulfate, reduced *in vacuo*, then purified by flash chromatography on silica (20% acetone in dichloromethane) to give the desired product as a colorless liquid; 163.5 mg (58.2 %). ^1H NMR (300 MHz, CDCl_3) δ 7.51-7.55 (m, 2H), 7.23-7.27 (m 2H), 3.96-4.13 (m, 4H), 2.73 (t, 2H, $J = 7.5$ Hz), 1.83-1.97 (m, 2H), 1.63-1.74 (m, 2H), 1.27 (t, 6H $J = 7.1$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 146.7, 132.2, 129.3, 118.9, 110.0, 61.6, 61.5, 36.5, 36.3, 25.9, 24.0, 23.8, 23.7, 16.5, 16.4; ^{31}P NMR (121 MHz, CDCl_3) δ 31.3; HRMS (FAB^+) calculated for $[\text{C}_{14}\text{H}_{21}\text{O}_3\text{NP}]$ ($[\text{M}+\text{H}]^+$) 282.1259, found 282.1262.

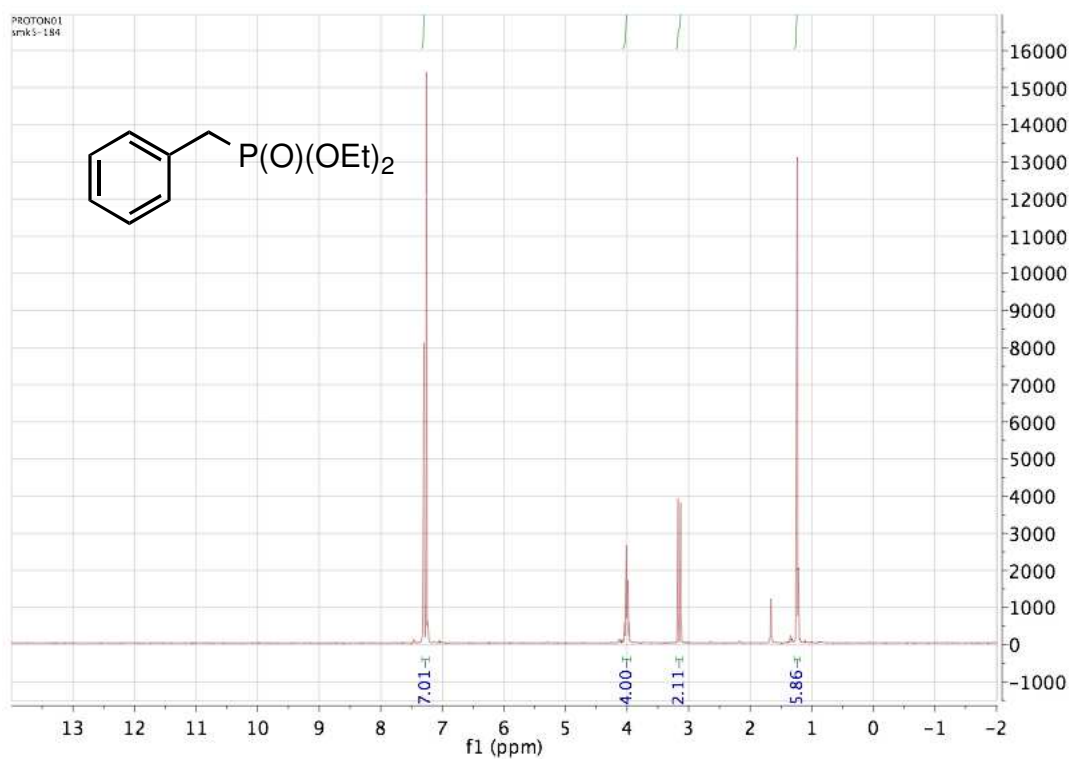
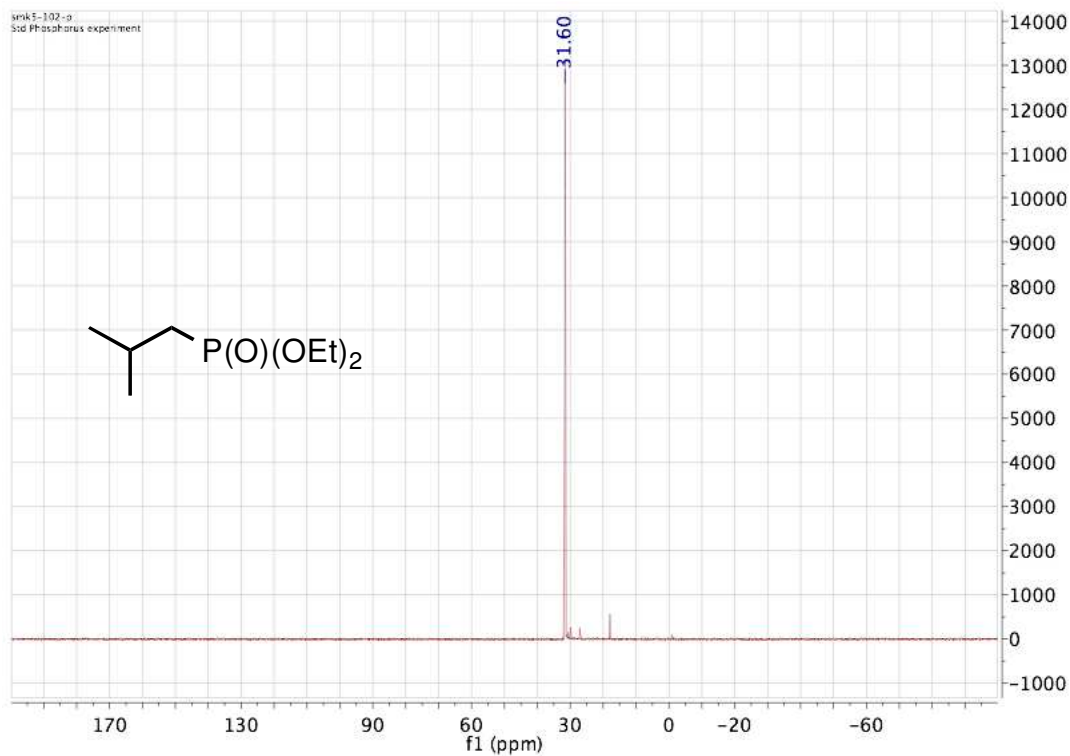
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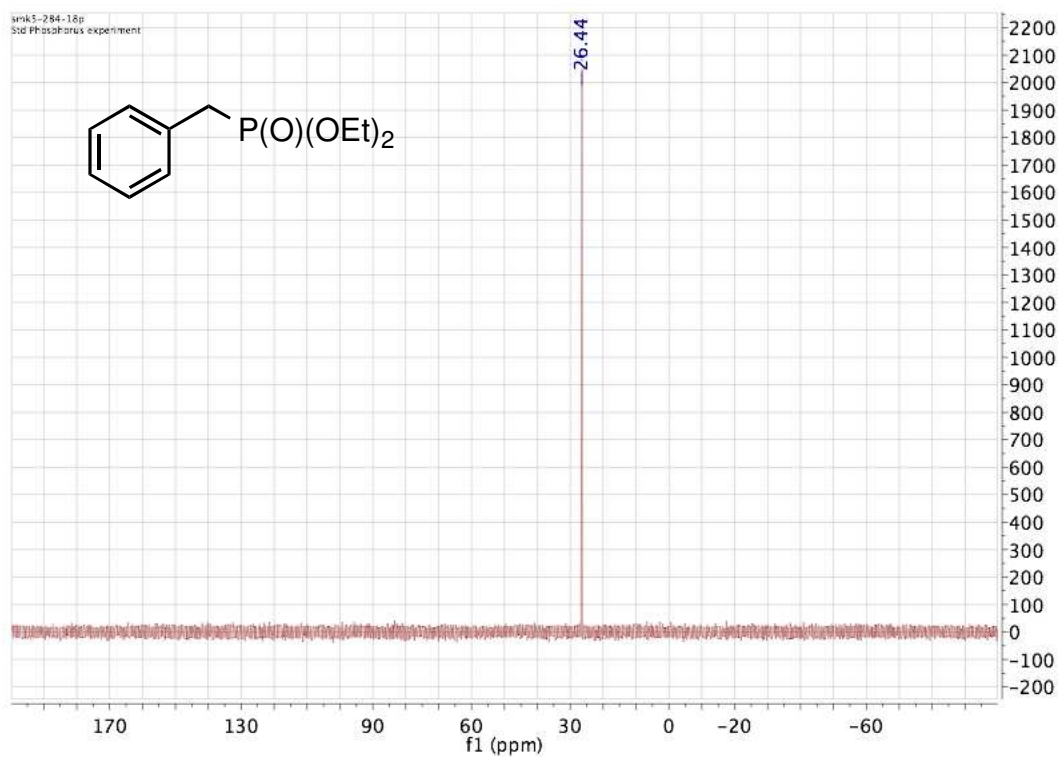
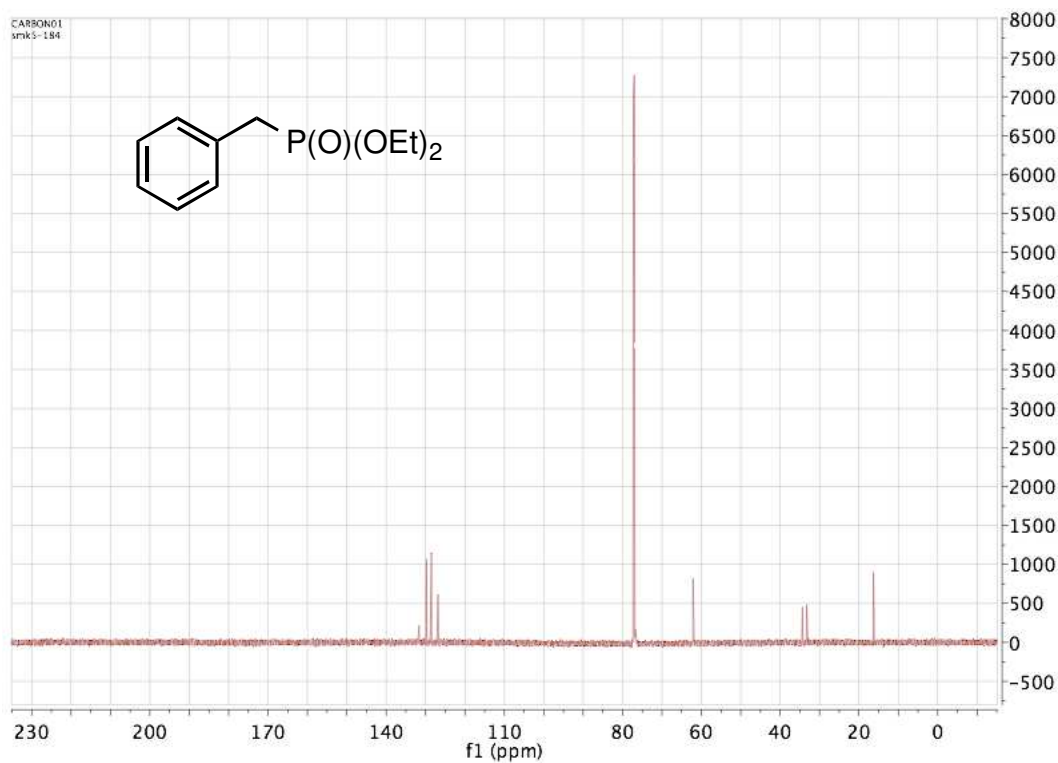


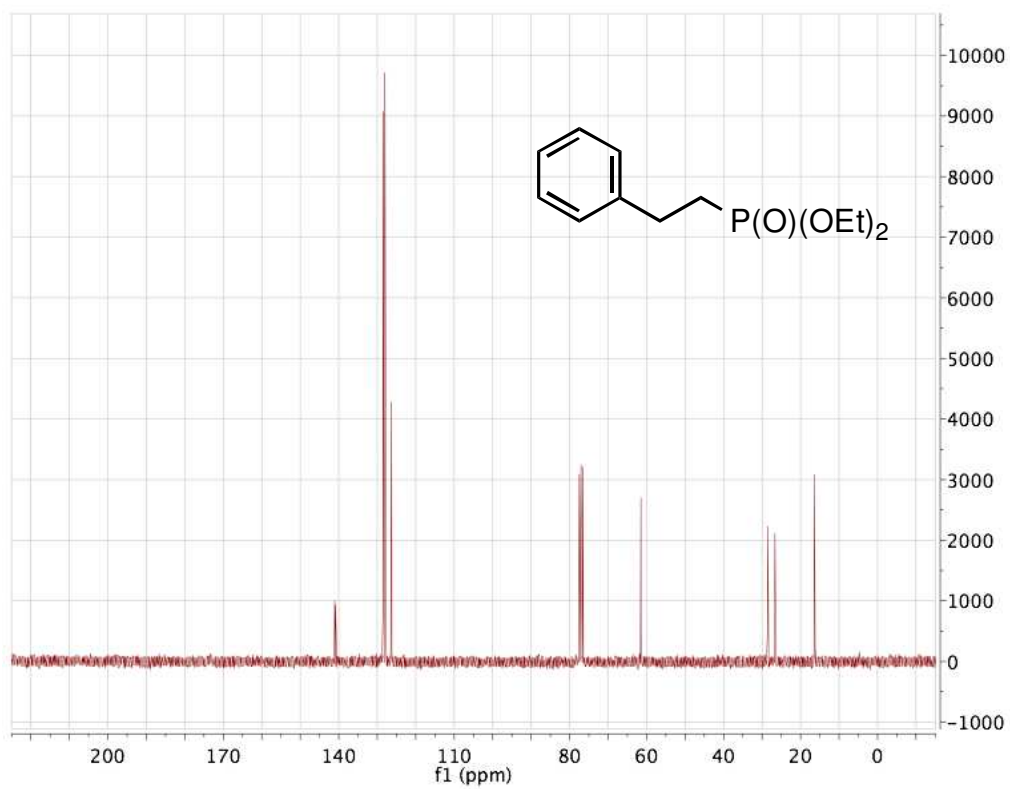
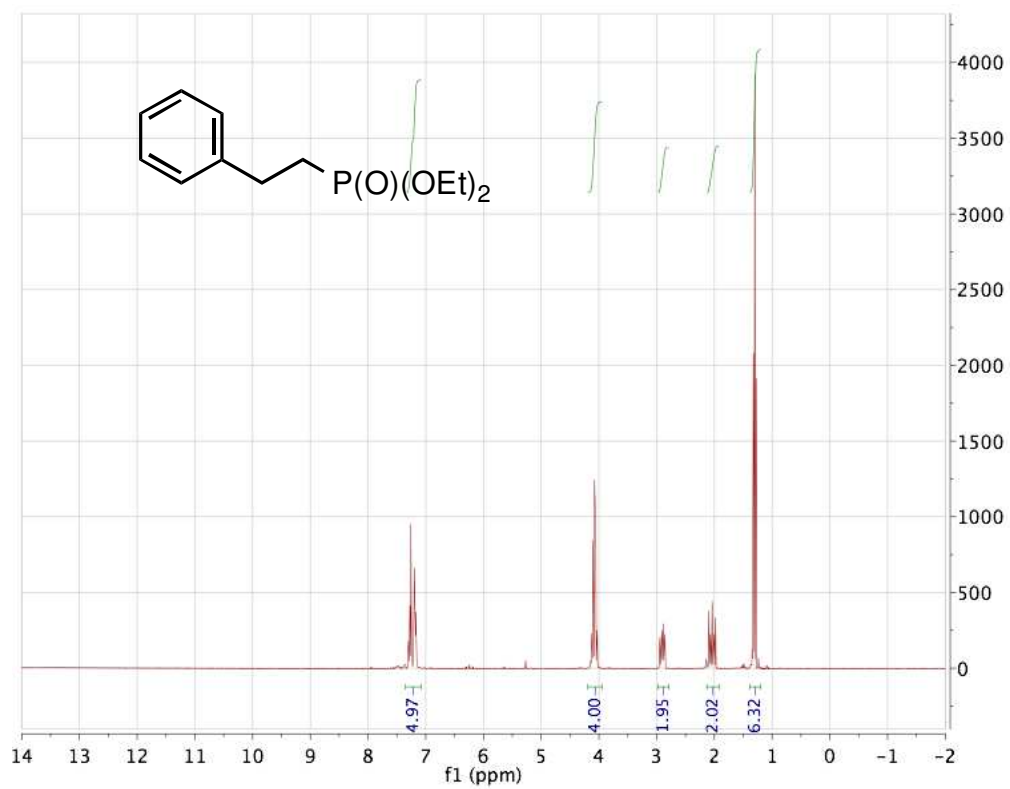


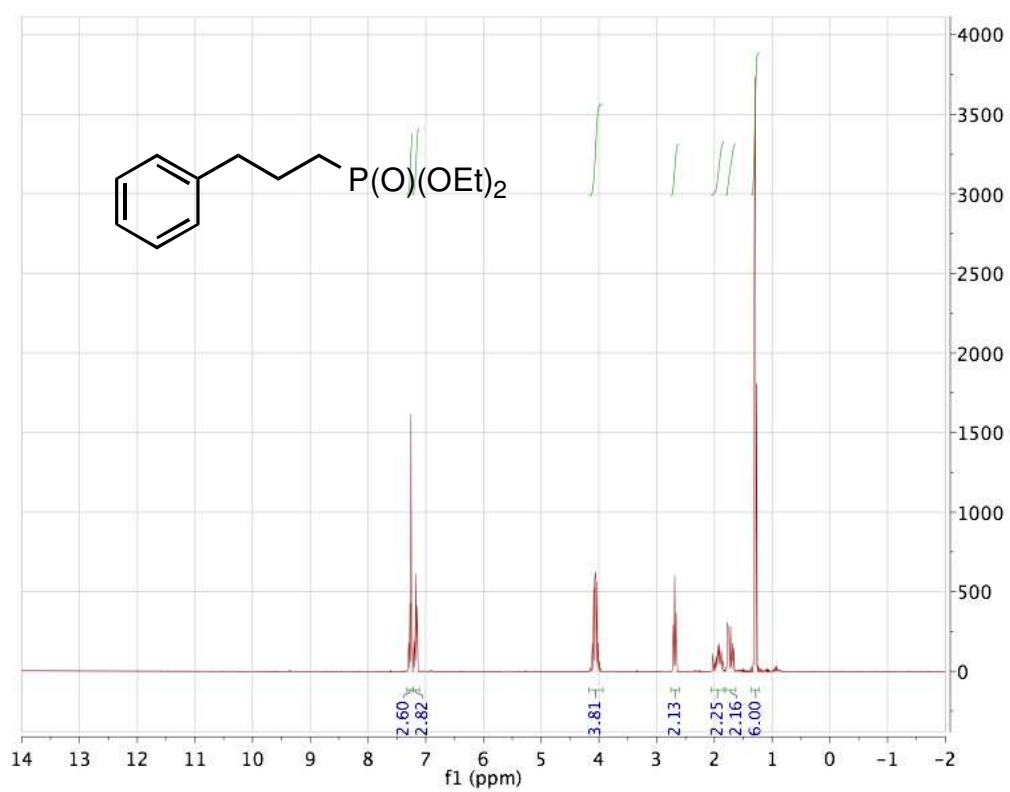
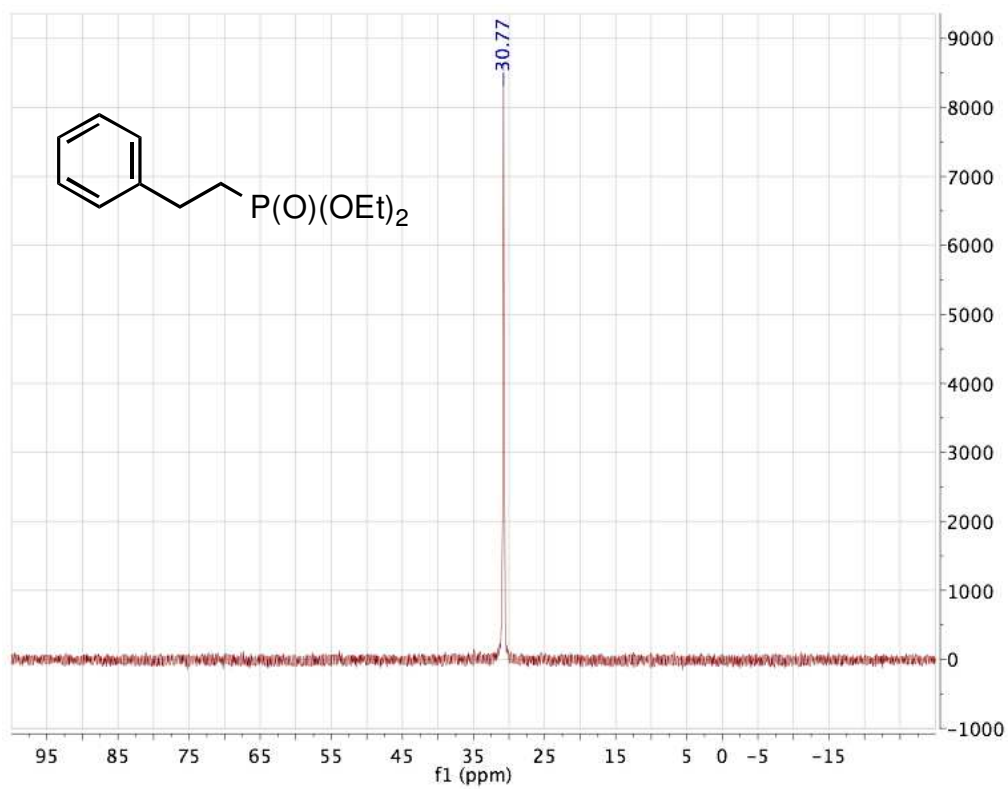


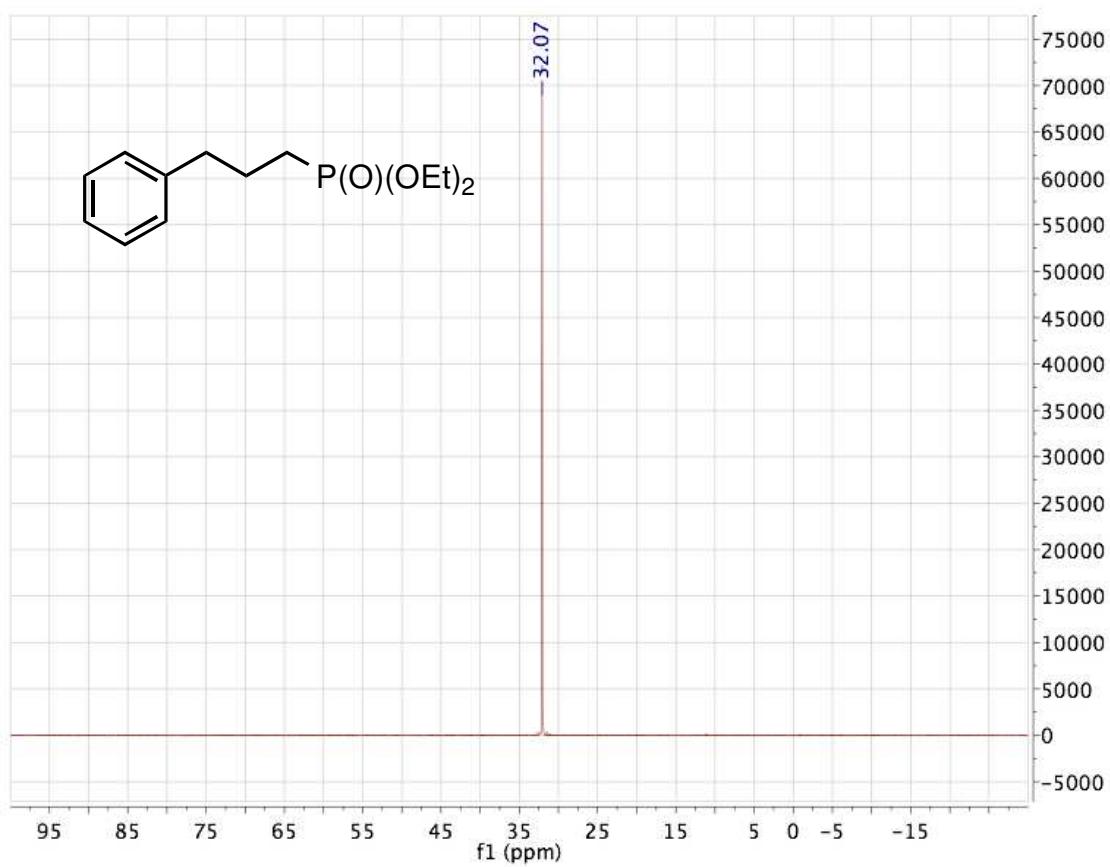
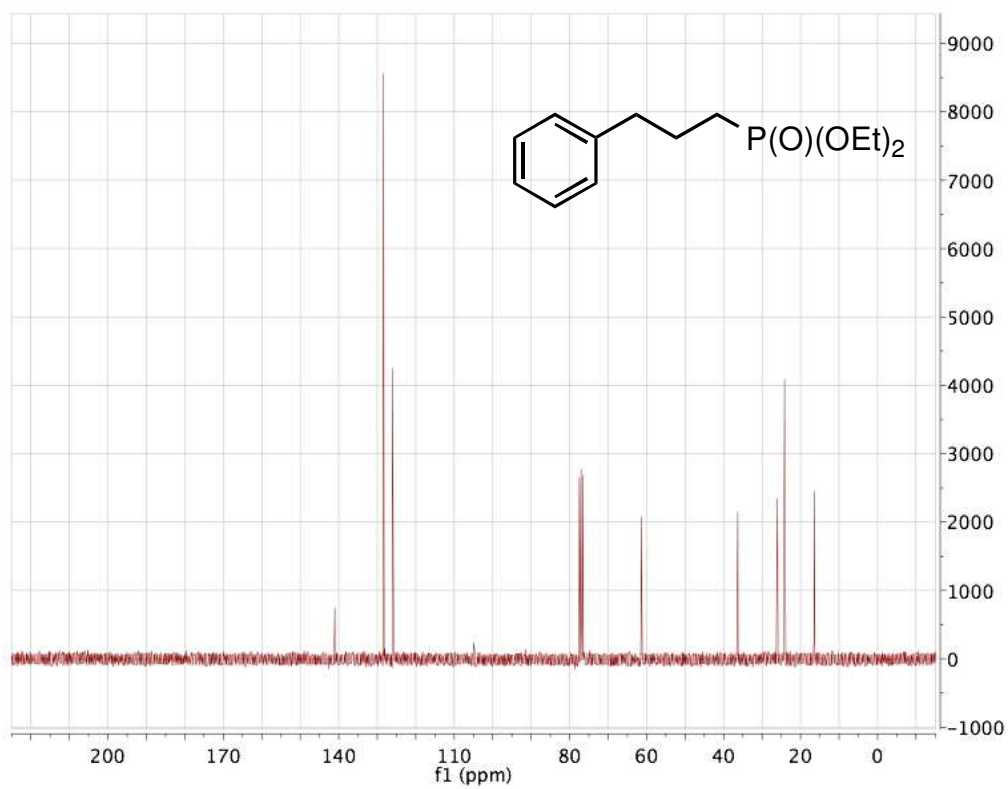


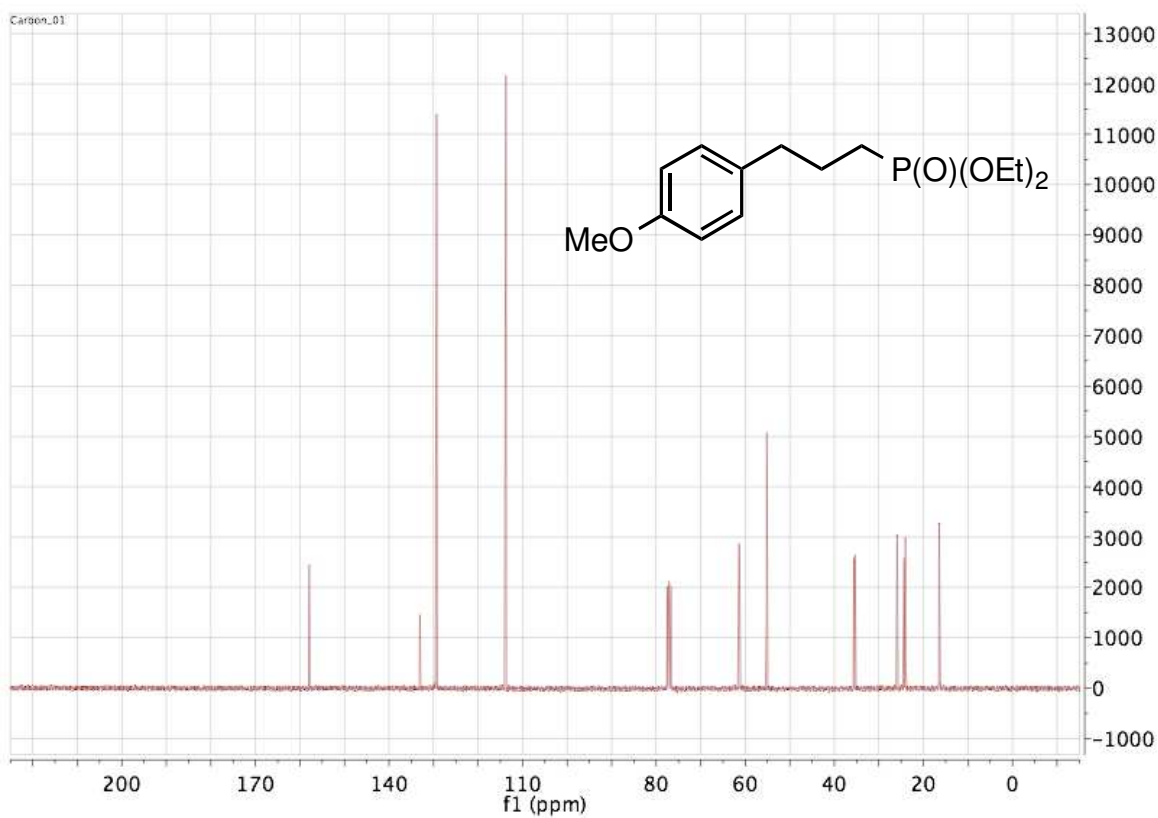
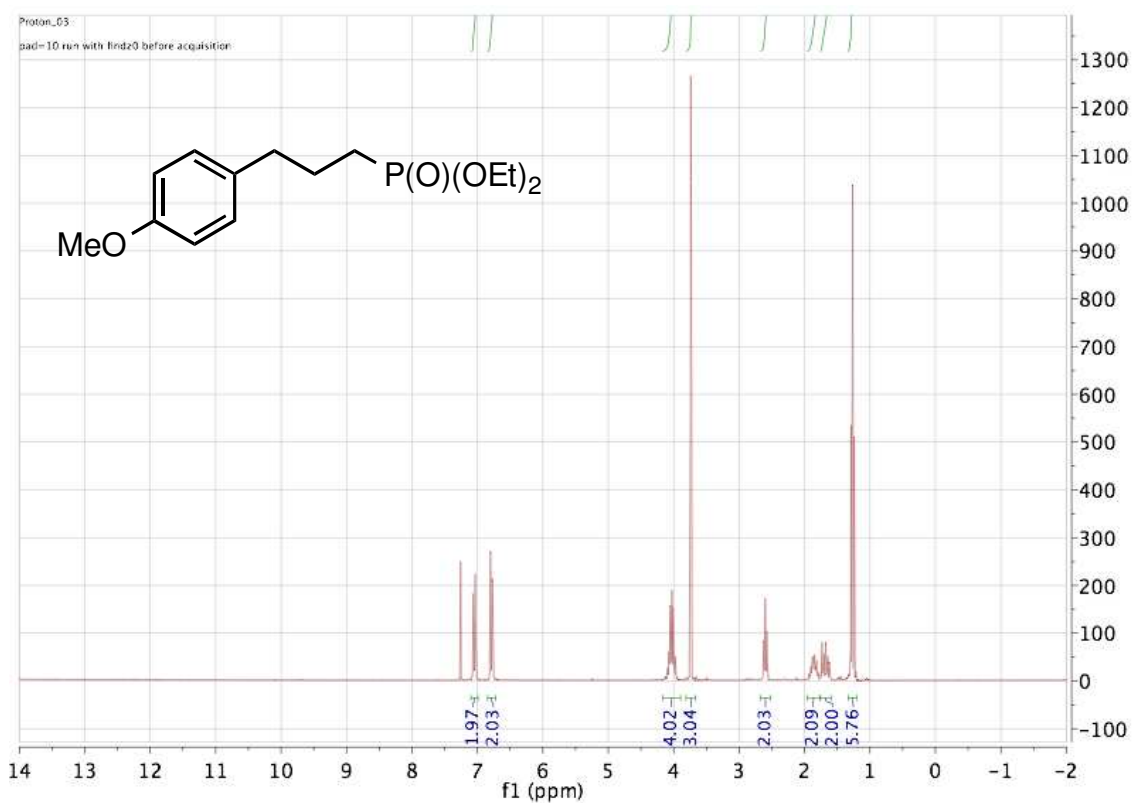


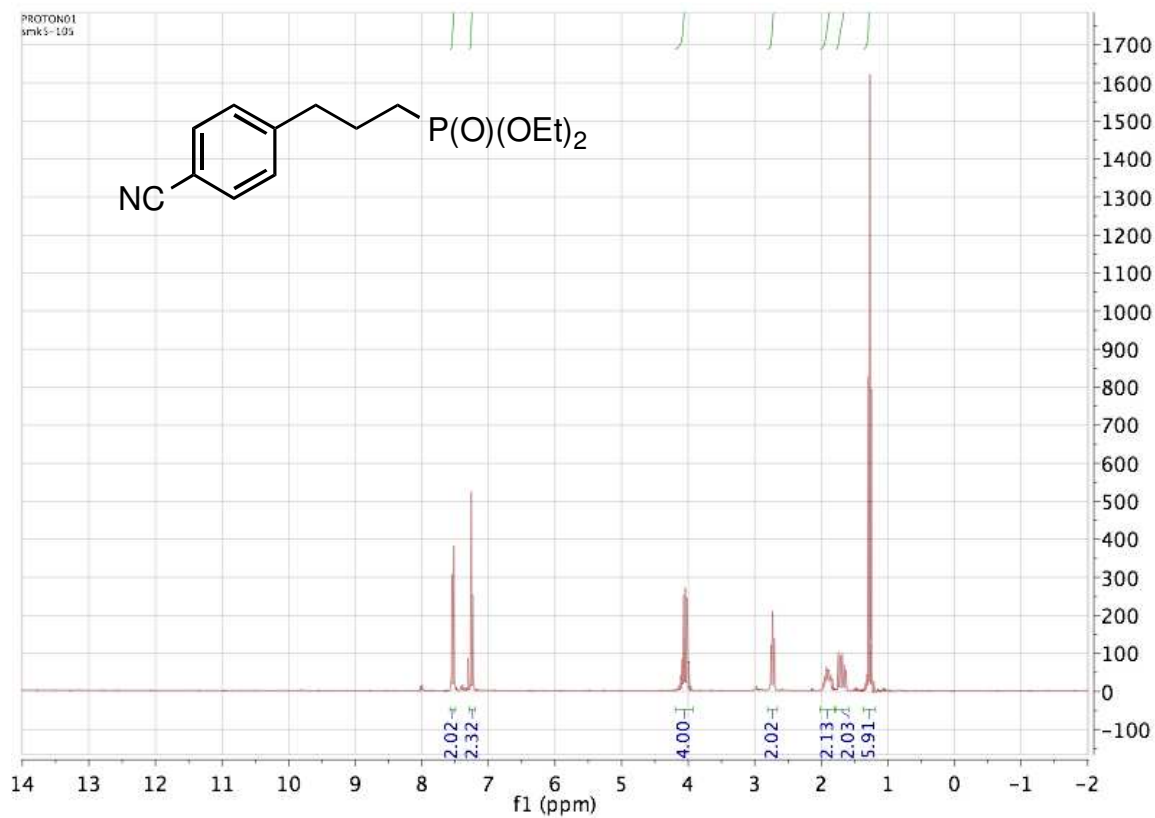
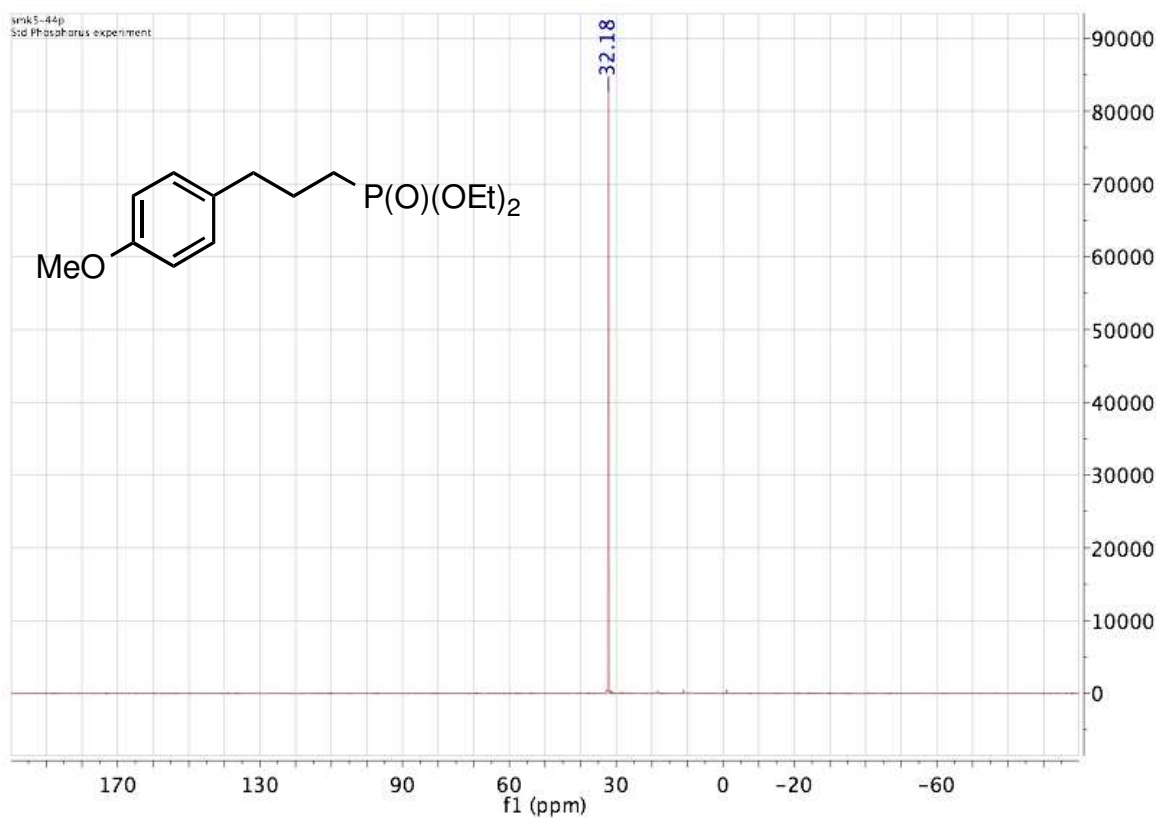


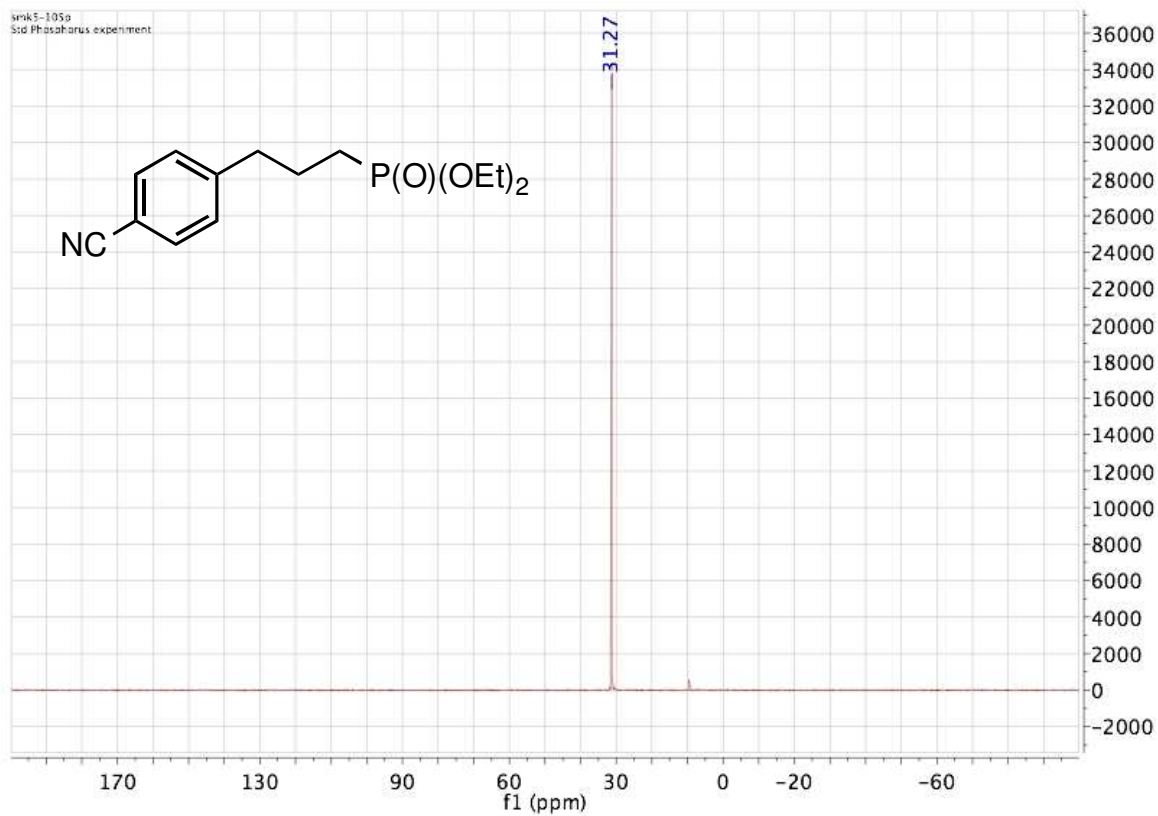
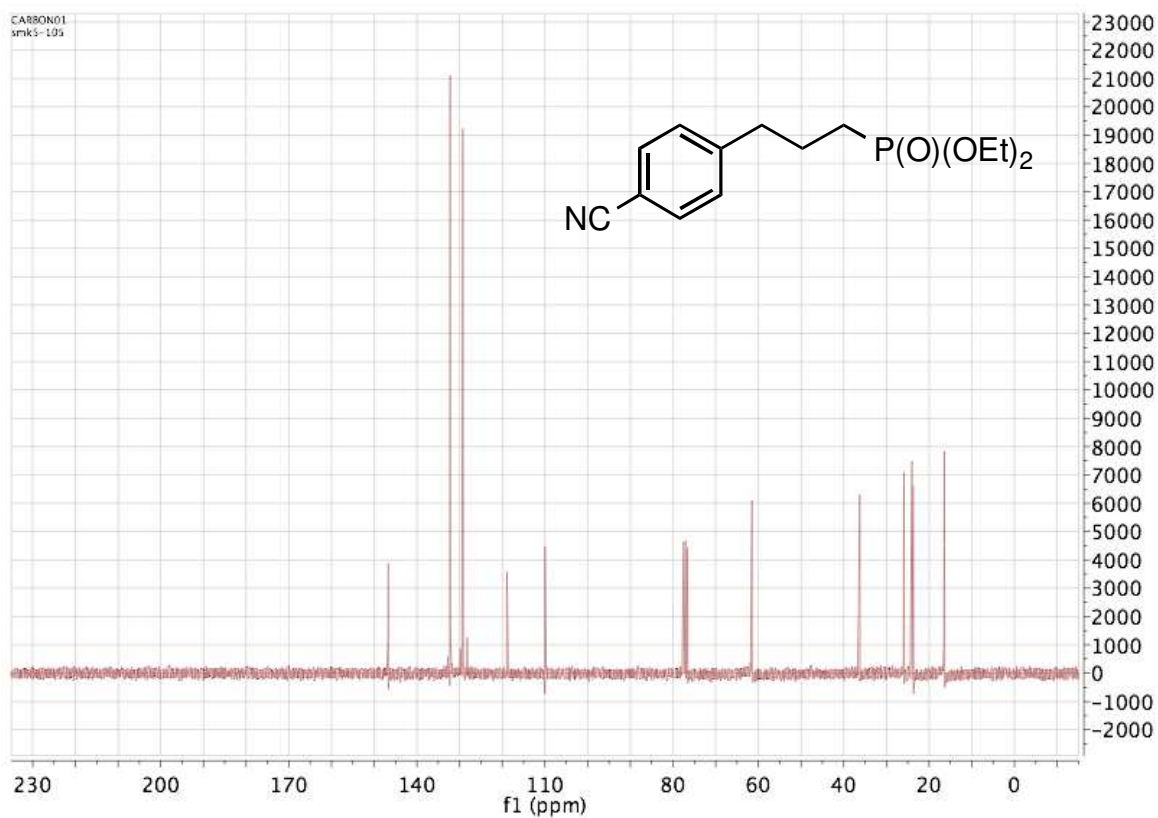












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